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REVIEW OF THE U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY TOXICOLOGY DIVISION

NATIONAL RESEARCH COUNCIL
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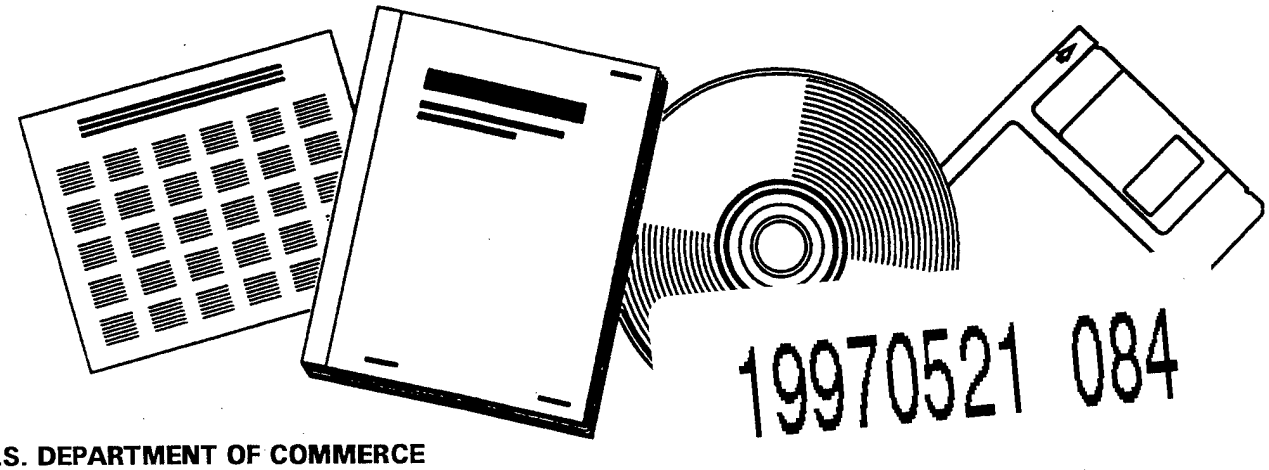

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Review of the U.S. Army Environmental Hygiene Agency Toxicology Division

COMMITTEE ON TOXICOLOGY
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The U.S. Army Environmental Hygiene Agency (AEHA) supports the preventive medicine program of the Army, especially in the area of occupational health and environmental toxicology. AEHA receives numerous requests to evaluate potential toxicological hazards associated with Army materials. In response to such requests, AEHA develops and reviews toxicological data and makes recommendations of acceptable exposures to these materials based on their potential to produce toxic effects in humans. The U.S. Army's Surgeon General's office requested the National Research Council's Committee on Toxicology (COT) to review the adequacy of the AEHA toxicology program. In response to this request, COT organized the Subcommittee on the U.S. Army Environmental Hygiene Agency Toxicology Program. The subcommittee evaluated the AEHA processes by critically reviewing the written material that describes the processes leading to recommendations for safe handling of equipment and materials, including the selection of specific toxicological tests on materials or chemicals, the procedures of health hazard assessment, and the activities associated with quality assurance. The subcommittee believes its recommendations will improve and strengthen the AEHA toxicology program and help AEHA to aid the Army's efforts related to preventive medicine.

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Subcommittee on the U.S. Army Environmental
Hygiene Agency Toxicology Program

Committee on Toxicology
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

The U.S. Army Environmental Hygiene Agency (AEHA) supports the preventive medicine program of the Army, especially in the area of occupational health and environmental toxicology.

AEHA receives numerous requests to evaluate potential toxicological hazards associated with Army materials. In response to such requests, AEHA develops and reviews toxicological data and makes recommendations of acceptable exposures to these materials based on their potential to produce toxic effects in humans.

The U.S. Army's Surgeon General's office requested the National Research Council's Committee on Toxicology (COT) to review the adequacy of the AEHA toxicology program. In response to this request, COT organized the Subcommittee on the U.S. Army Environmental Hygiene Agency Toxicology Program.

The subcommittee evaluated the AEHA processes by critically reviewing the written material that describes the processes leading to recommendations for safe handling of equipment and materials, including the selection of specific toxicological tests on materials or chemicals and the activities associated with quality assurance. The subcommittee believes its recommendations will improve and strengthen the AEHA toxicology program and help AEHA to aid the Army's efforts related to preventive medicine.

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1 *Introduction*

The National Research Council's Committee on Toxicology (COT) was asked to review the toxicology program of the U.S. Army Environmental Hygiene Agency (AEHA) and the activities of the AEHA's Toxicology Division. This report provides a review of the program and presents recommendations to improve the division's activities.

The AEHA is a large organization, of which the Toxicology Division is a small part. The division is charged with identifying the potential hazards to military and civilian personnel arising from the use of military equipment and materials that may involve exposure to toxic chemicals. As a toxicity-evaluating agency, AEHA is the focal point in occupationally and environmentally related primary disease prevention.

According to its mission, AEHA:

> Supports worldwide preventive medicine programs of the Army and other Department of Defense and Federal agencies where agreements exist or when directed by the commander of Health Services Command, Office of the Surgeon General, or Department of the Army through consultations, supportive services, investigations, and training to accumulate, evaluate, store, and disseminate data in the areas of environmental quality, occupational and environmental health, toxicology, radiation and environmental sciences, pest management, and laboratory services.
>
> Reviews occupational, environmental, safety, and health documents [i.e., *Federal Register*, U.S. Environmental Protection Agency guidelines, Occupational Safety and Health Administration standards, National Institute of Occupational Safety and Health criteria documents, National Research Council proposed and final rulings].

> Serves as the Army's preventive medicine program executive agency for the development and publication of occupational and environmental health documents, technical publications, standards, and their related forms. Conducts an accredited residency training program in occupational medicine.
>
> Conducts postgraduate courses and workshops in environmental and occupational health; industrial hygiene; hearing conservation; ionizing radiation protection, laser and microwave hazard awareness; entomology and pesticides and environmental chemistry.

AEHA receives numerous requests to evaluate potential toxicological hazards associated with Army materials. Requests are of three types:

- Requests involving a health hazard assessment (HHA), which employs existing toxicological, clinical, and epidemiological data. The HHA was developed to examine the potential toxicological hazards of an Army-specific system operated by military personnel and at times by civilians.
- Requests involving toxicity clearance (TC) of a new product into the military supply chain. This product may have been developed either by the military or by the private sector and may be produced commercially. Such new products have potential health effects on military and civilian populations and thus must be cleared before they can enter the military supply chain.
- Requests involving a military specification review (MSR), in which military and federal specifications and standards are evaluated.

These specifications and standards become particularly important during the purchase of manufactured materials by the U.S. Department of Defense (DOD) and the federal government for military applications. Safe-handling practices are developed from the HHA, the TC, and the MSR, and protective guidelines are instituted from them.

The COT's Subcommittee on the U.S. Army Environmental Hygiene Agency Toxicology Program reviewed two categories of AEHA activities. The first category is concerned with the process for determining which toxicological tests to perform. The subcommittee had two tasks for this category: (1) critically review the decision-making

process leading to selection of specific toxicity tests on materials or chemicals by AEHA's Toxicology Division; and (2) review quality-assurance procedures (QA) associated with the test-selection process. The second category of activities involves the procedures for using toxicological data in HHAs. The subcommittee's task for this category was to review and comment on these procedures.

This report of the subcommittee addresses the above areas and recommends guidance to the AEHA Toxicology Division on the analyses and interpretation of toxicity studies to aid the AEHA in accomplishing its mandate.

The subcommittee met with personnel of AEHA and its Toxicology Division at a site visit to Edgewood Area of Aberdeen Proving Grounds in Edgewood, Maryland, on June 29-30, 1989. AEHA submitted five sets of documents for subcommittee review and reference in responding to the task assignment. These and other specific papers requested by the subcommittee are listed in Appendix 1 and are discussed in other chapters of this report.

The three major processes involving AEHA's Toxicology Division—the HHA, TC, and MSR—require an understanding of the potential toxicity of materials and are likely to involve the performance of hazard and risk assessments. Personnel performing these evaluations must identify the toxicity associated with the materials, review the data that exist on the toxicity, recommend additional toxicological tests when needed, define potential exposure scenarios, and use the information collected to conduct a risk assessment. Other key activities associated with the above processes are QA, record keeping, and cooperation and communication with AEHA, military, and civilian personnel who contribute to the overall evaluation.

AEHA and its Toxicology Division have other functions that are not the immediate concern of this report. For example, the AEHA provides advice to the Surgeon General on data and systems analysis pertaining to the adequacy of the clean-up activities performed under the Defense Environmental Restoration Act, which is the military equivalent to the Environmental Protection Agency's Superfund activity.

For this report, the subcommittee has critically reviewed written documents provided by AEHA and its Toxicology Division that describe the processes leading to recommendations for safe handling of equipment and materials, including the selection of specific toxicological tests on materials or chemicals, the procedures for HHA, and the

activities associated with QA. No written procedures were available on AEHA's health risk assessment (HRA) process.

The report is divided into three parts. Chapter 2 describes a continuum of techniques (a series of activities that overlap to provide an overall health and safety program) that are useful in the prevention of occupational and environmental disease. An evaluation is made of the AEHA Toxicology Division's role in this continuum. Chapter 3 is a review of papers supplied to the subcommittee (Appendix 1) in response to the statement of task. Chapter 4 discusses the establishment of peer review and a science advisory panel to help ensure the proper functioning of the activities described in Chapter 2 and the quality of toxicological assessment activities reviewed in Chapter 3.

2 *Integration of AEHA Approaches to Assessments Related to Health and Toxicology*

The subcommittee described a continuum of techniques (a series of activities that overlap to provide an overall health and safety program) (Table 1) that pertain to prevention and then evaluated AEHA's program of prevention of disease originating from occupational and environmental exposures by determining AEHA's use and implementation of each technique, the contribution of the Toxicology Division to each segment of the continuum, and the degree of integration of the program within AEHA as it relates to the continuum.

The major topics in the continuum are ranked in order of importance. The techniques listed first are those for primary prevention and those listed later are for secondary and tertiary prevention. Primary prevention involves preventing the occurrence of diseases, secondary prevention involves minimizing the effect of diseases when they are not yet clinically symptomatic through early identification and intervention, and tertiary prevention involves minimizing the effects of diseases through the delivery of appropriate medical care to afflicted individuals (Last et al., 1980).

Two important overarching techniques are not listed at any point in the continuum because they are pervasive. These two techniques are surveillance and priority setting. Surveillance is the ongoing collection, analysis, and use of health data for the purposes of prevention. In the ordered continuum, health data should be collected at every level, analyzed, and employed to improve the use of any prior technique in the continuum. For example, data on the occurrence of adverse health effects should be used to indicate need for additional toxicological testing, which appears early in the continuum. In addition, a systematic approach is needed in reviewing and testing chemicals to prevent disease or injury. For AEHA and the Toxicology Division, this approach implies a coordinated transfer of information within the agency, as well as among other agencies responsible for other parts of the continuum.

Table 1 The Roles of AEHA and Its Toxicology Division in the Continuum

Continuum Tasks	Relationship to AEHA's Toxicology Division
Pre-acceptance Product Evaluation	
Hazard Evaluation	1
Product Testing	1
Exposure Assessment	2
Risk Assessment	1,2
Risk Management	
Elimination	2
Substitution	2
Permissible Exposure Limitation	1,2
Post-acceptance Evaluation	
Environmental Monitoring	2
Personal Monitoring	2
Biological Monitoring	2
Medical Screening and Epidemiological Evaluation	2
Medical Care and Rehabilitation	2

1 = Principal role for AEHA Toxicology Division personnel.
2 = Supporting role for AEHA Toxicology Division personnel (i.e., communicating information generated during pre-acceptance product evaluation to others who will use such information to make risk management, monitoring, and medical decisions) who need to receive information concerning these tasks from other sources to complete their principal responsibilities successfully.

The second overarching technique is priority setting. AEHA must make decisions on the basis of the benefits of prevention of disease associated with some exposures in contrast to other exposures. Priorities are set by identifying the hazards and then ranking the order in which the exposures are addressed. From a practical standpoint, priority setting occurs whether or not a formal system is in place. Efficiency can be increased and institutional memory enhanced if decisions are made according to an ordered, well-documented process. In addition, a formal system would help to ensure consistency in evaluation.

Brief descriptions of the techniques presented in Table 1 and used in the continuum of prevention appear below.

PRE-ACCEPTANCE PRODUCT EVALUATION

An agent should be evaluated for hazard before its use, and anticipated exposure to the agent should be defined. AEHA uses these requirements in the TC process as follows:

- *Hazard Evaluation.* Hazard evaluation involves an assessment of the innate toxicity of an agent, based on the structure, and toxicity of similar agents. Based on the hazard evaluation, use of the product may be abandoned or considered further. In the latter case, product testing may be considered. During hazard evaluation, decisions are reached on whether toxicological testing is needed and whether alternatives to the agent in question are available.
- *Product Testing.* Based on the hazard evaluation, the product may be tested in studies that range from in vitro experiments to whole animal bioassays. In this stage, decisions are made on which toxicological tests to conduct. Then the experiments are performed, and the data are analyzed. The choice of toxicological tests should be based on an evaluation of all potential exposure situations, or if exposure potential is unknown or uncertain, a thorough battery of toxicological tests should be conducted. Results from product testing should be compared with human experience during use through medical surveillance.
- *Exposure Assessment.* Exposure is defined in terms of the intended use of the materials and includes development of ranges of exposure estimates through modeling or direct monitoring. Such an assessment should include the potential exposure scenarios and identification of any highly exposed populations or those possibly at increased risk due to special sensitivity.
- *Risk Assessment.* Results of toxicological tests, information about related materials, and the potential for exposure are used to evaluate the probability of health risk due to use of the candidate product. Risk assessment should be clearly defined in terms of whether it is based on average exposure, the highest exposed individual, exposure of sensitive subpopulations, or other exposure scenarios. It should also include an evaluation of the level of confidence in the data and should identify uncertainties in the hazard evaluation,

product testing, exposure assessment, and risk estimate. The end product of risk assessment should be a document that clearly identifies the processes used and the assumptions upon which the assessment is based.

RISK MANAGEMENT

Based upon the risk assessment, availability of alternatives, and potential benefits, decisions are made on the limits of use of the candidate agent. Three standard approaches include:

- *Elimination.* The potential risk may be so great or the anticipated benefits so limited that use of the material cannot be justified.
- *Substitution.* The potential risk outweighs the potential benefits, but the benefits may be such that an alternative, less hazardous agent should be used, if available.
- *Permissible Exposure Limitation.* Exposure to the agent in question may be limited to levels below those believed to present a risk. The primary and preferred approach to control of exposure is through engineering controls (such as exhaust ventilation) when exposure should be limited but substitution or elimination of the agents is not feasible. Personal protective devices may be necessary to control exposure adequately when engineering controls cannot provide an environment consistent with risk-management decisions; their use, however, is to be considered a last resort.

POST-ACCEPTANCE EVALUATION

Once the product is in use, the following methods are employed to validate the pre-acceptance procedures of hazard evaluation, product testing, exposure assessment, risk assessment, and risk management.

- *Environmental Monitoring.* The purposes of environmental monitoring are to help gauge the adequacy of exposure controls and to identify areas where additional protection is necessary.
- *Personal Monitoring.* Monitoring of the exposed worker further assesses the adequacy of engineering controls and helps to define when personal protective devices are needed.
- *Biological Monitoring.* Biological monitoring using validated

procedures provides an indication of the level of toxicant, its metabolites, or its reaction products in body or body fluids. Such levels may serve as biological markers of exposure or disease and may indicate the need for additional protective measures. These data also help in assessing workplace-associated changes in the health of exposed workers (both individuals and groups) identified in medical screening.

- *Medical Screening*. Medical screening is the periodic examination of exposed individuals to identify early signs and symptoms of disease before they are clinically apparent. The role of medical screening is to enhance the potential benefit of medical intervention to the person screened and to ensure that the methods for controlling exposure and establishing the level of permissible exposure are adequate.

MEDICAL CARE AND REHABILITATION

Medical care and rehabilitation involve providing appropriate medical care and assisting in the recovery of those suffering from occupational and environmental disease.

The continuum described above is not novel. It reflects the normal responsibilities and interactions of toxicologists, industrial hygienists, and medical personnel. Unfortunately, the tasks of these professions are sometimes compartmentalized, rather than viewed as part of a continuum. When the techniques are viewed as a continuum, information collected at each stage is widely communicated and should affect further decisions throughout the continuum. This is the essence of surveillance, which is the collection, analysis, and use of health data for the purposes of prevention of disease. In evaluating hazard and risk assessment programs, it is important to assess not only the effectiveness of each technique in the continuum but also the relationship of each technique to the whole.

The subcommittee has identified the AEHA Toxicology Division's role as either principal or supporting in the continuum of tasks shown in Table 1. The Toxicology Division has a key role in pre-acceptance product evaluation (hazard evaluation, product testing, and risk assessment). Toxicology Division personnel have a supporting role in maintaining communication among those who address exposure assessment, risk management, post-acceptance evaluation, and medical care and rehabilitation.

RECOMMENDATIONS

The following recommendations were made by the subcommittee to help support the integrity of AEHA scientific activities:

(1) The AEHA Toxicology Division should develop standard operating procedures for its activities in relation to each of the continuum tasks. Particular attention should be given to those tasks for which the Toxicology Division has principal responsibility. The Toxicology Division should review standard operating procedures for which it has secondary responsibility to ensure proper integration into its activities.

(2) AEHA departments should systematically review their procedures and augment them as necessary and maintain the flow of information among various departments to better accomplish their objectives as defined by the continuum tasks.

(3) AEHA is only one of several Army or DOD organizations that may contribute to the health assessment of military materials. Management systems within DOD should be clearly directed and communicated among all appropriate military organizations to ensure coordination, reduce duplication, and achieve integration of the processes for selecting and interpreting toxicological and health-related tests. In particular, AEHA should be made aware of hazard determinations and risk assessments (if any) that are conducted by other DOD organizations. In addition, AEHA should thoroughly evaluate existing information from other government agencies, other organizations, and the open literature prior to conducting its own toxicity determination. This procedure would avoid duplication of effort and be cost effective.

3 *Review of AEHA Processes Associated with the Toxicology Division*

AEHA's director of occupational and environmental health divided the activities of the Toxicology Division into three categories. These and the subcommittee's tasks in each category are the following.

Category 1 activities concern the decision process for determining which toxicological tests to perform. The subcommittee tasks are twofold: (1) Critically review the AEHA decision-making process leading to selection of specific toxicological tests on materials or chemicals by AEHA's Toxicology Division. (2) Review QA procedures associated with the test selection processes. This category and tasks concern pre-acceptance product evaluation, which is defined in Chapter 2.

Category 2 involves setting up protocols for specific toxicological tests. No subcommittee review of specific protocols was requested.

Category 3 activities are to review procedures for use of toxicology data in health hazard assessments (HHAs). The subcommittee task was to review and comment on the procedures used for HHAs.

Five sets of documents were submitted by AEHA for subcommittee review; they are listed in Appendix 1. The documents were reviewed by the subcommittee and pertinent information was identified for use in evaluating the categories and tasks previously defined. Those documents considered pertinent to each task are briefly reviewed in the following summary. Recommendations were made for each category and task on the basis of information contained in the documents and, in some cases, on clarifications obtained in discussion with the Office of the Surgeon General and AEHA personnel.

SUBCOMMITTEE RESPONSE TO CATEGORY 1, TASK 1

The AEHA Toxicology Division plays a principal role in selecting and evaluating toxicity tests. The selection of specific toxicological

tests is directed by the purpose for which the material is being reviewed. It is of paramount importance that the purpose be clearly understood before selecting specific tests. Defining the specific tests and protocols requires a thorough knowledge of an agent's (known) physical, chemical, and toxicological properties, the potential route of human exposure during use, and the identification of data gaps. Such knowledge will help to dictate testing parameters (such as the choice and number of animals or strains or in vitro techniques), dose levels, route of exposure, duration of the study, and end points to evaluate. For example, if the primary route of exposure to an agent is dermal contact, then an ingestion study may not be appropriate unless it is clearly shown that dermal absorption is rapid and complete, and metabolic processes and target organ exposures are comparable.

Also essential in defining the question is consideration of how the data from studies will be used. For example, if the data are to be used for understanding the inherent toxicity of a chemical, the choice of tests would be different from those used for quantitative risk assessment. In practice, however, experiments often are designed so that both goals are addressed simultaneously to achieve cost effectiveness.

The relevant documents submitted by AEHA are listed in Appendix 1. Those reviewed for test selection are the Standard Operating Procedure for Toxicity Clearance, the Division QA Plan, and the Draft QA Plan (AEHA, 1983, 1988a, 1989a, respectively).

AEHA supplied no material defining what constitutes adequate data regarding an agent's toxicity or how decisions are made as to what toxicological tests are to be performed when data are insufficient. The Standard Operating Procedure for Toxicity Clearance indicates that some decisions are made concerning the adequacy of data for a TC, but it does not specify actions to be taken if the data are inadequate. The Draft QA Plan and the Division QA Plan indicate that the Toxicology Division's QA plan includes a number of standards for laboratory operation, such as the Toxic Substances Control Act Test Guidelines. However, such guidelines do not outline a strategy for test selection for agents.

The overarching goals of the continuum discussed in Chapter 2 are priority setting and surveillance. Systematic priority setting was not evident to subcommittee members in the cursory overview of AEHA's Toxicology Division during the June 29-30, 1989, visit to AEHA at the Edgewood Area of Aberdeen Proving Grounds. Instead, critical issues appeared to be addressed as they arose. Since the Toxicology Division plays a supporting role in surveillance activities in AEHA,

the primary responsibility for surveillance activities lies elsewhere and these were not reviewed in detail by the subcommittee.

SUBCOMMITTEE RESPONSE TO CATEGORY 1, TASK 2

The goal of reviewing documents on QA was to determine whether such documents define a complete QA process.

Although there were several documents dealing with QA in the material provided, none of them dealt directly with the test selection process or use of data. The 1987 QA Plan (AEHA, 1987, Appendix 1) presents procedures for an audit trail, organization, and responsibilities. The document applies to technical correspondence, reports, analytic evaluations, and mission-related contractual services. It also includes Toxicology Division-developed QA documents that consist of lists of standard operating procedures. The plan states that "the procedures in effect are based on published Federal guidelines and were designed to satisfy registration requirements for both the U.S. Environmental Protection Agency and the Food and Drug Administration." No specific references are given, and there is no indication of the decision process for test selection.

The 1989 Draft QA Plan is a document that is intended to provide guidance for implementation of a QA program and gives detailed guidance for implementation of AEHA Regulation 702-1 (AEHA, 1989b, Appendix 1). The final document will be broader in scope than the 1987 QA Plan in that it will cover data production and analysis, technical review, management review, and documentation.

Appendix C of the Draft QA Plan is to be a collation of the Toxicology Division's QA documents. The 1988 Division QA Plan apparently will become part of Appendix C. Appendix D of the Draft QA Plan will describe documentation for QA but is essentially a guideline for good laboratory practices (GLP); however, it does not refer to any published GLPs. (It also permits pencil entries, which generally are not permitted without justification under EPA or FDA regulations.)

The Analytical QA Program (AEHA, 1982, Appendix 1) contains Appendix D, the Toxicological Assessment Program, which covers technical QA for laboratory procedures, but does not address test selection. The Division QA Plan is discussed in "Subcommittee Response to Category 1, Task 1" above. The QA Review (AEHA, 1989, Appendix 1) is a memorandum containing notes on a QA review

of laboratory procedures by Timothy L. Fisher, chief of the Analytical QA Division. The memorandum is brief, indicates some problems, but also indicates compliance with the relevant standards. The memorandum does not address appropriateness of the test procedures or make recommendations concerning problems noted. The following reports listed in Appendix 1 relate to animal care or animal care facilities: Table V in Accreditation and Certifications of U.S. AEHA (AEHA, 1988b); Use of Animals in DOD Programs (DOD, 1984); Use of Animals for Medical Purposes (DOA, 1987); and the letter to Col. Frank E. McDermott (AAALAC, 1986). Review and accreditation by AAALAC was completed.

The Standard Operating Procedure for Toxicity Clearance (see Category 1, Task 1) addresses procedures and responsibilities, but does not give information about how decisions are made.

The report "Toxicity Clearance of Sequa Chemicals PRYM 200 Soil Release Treatment" (OTSG, 1989, Appendix 1) contains a memorandum from AEHA recommending approval of a soil release agent for external use on military clothing. The request for TC and other related letters and memoranda is included. From the documents supplied in the report, it is difficult to learn the extent of the review that actually occurred and that led AEHA to give its conditional approval. Although the request for clearance specifies evaluation from the standpoint of skin toxicity, it is not clear whether any skin toxicity data were evaluated. Clearance appears to have been based solely on unsubstantiated statements from the supplier.

The Draft QA Program (AEHA, 1989c, Appendix 1) is the draft report of Regulation 702-1 to establish AEHA's QA program. This regulation will prescribe policies and procedures for QA, assign responsibilities, establish mechanisms for audit trails, and require the development of written QA plans.

The HHA QA Incident Report (U.S. Army Health Hazard Assessment Office, 1989a, Appendix 1) provides an example of such a report and appears to be a good method for identifying unacceptable data or missing information that is needed to complete an HHA.

The HHA Report Checklist QA Program (AEHA, Undated(a), Appendix 1) is a simple checklist for tracking the HHA process.

The Appendix FF report on HHA projects (U.S. Army Directorate of Industrial Hygiene, Undated, Appendix 1) was listed as a QA plan but appears to be a guidance document from the directorate of industrial hygiene that addresses HHA reports. It indicates that the project officer should ensure that "all potential health issues are ad-

dressed," but no information is given on the health hazards to be considered or how to decide which hazards are relevant in a given situation.

The Occupational and Environmental Medicine Division QA Plan Outline (OEMD, Undated, Appendix 1) is a brief plan for AEHA to help assure that quality is maintained in its technical correspondence and report services.

The QA Plan, Internal Report (AEHA, Undated(b), Appendix 1) is a thorough set of QA procedures for AEHA's Health Physics Division. The plan includes requirements for traceability of calibration procedures for various defined project levels. Three points that are not included are record retention requirements, educational requirements for the QA officer, and external audit requirements for the QA activities.

The Bio-Acoustics Division QA Plan (AEHA, Undated(c), Appendix 1) is a general QA plan for the Bio-Acoustics Division. It allows for broad interpretation of practices by the division management, which appears to have responsibility for QA as opposed to an appointed QA officer. Four appendices are listed but not included.

The 1988 QA Plan, Laser Microwave Division (AEHA, 1988c, Appendix 1) is a general QA plan for the Laser Microwave Division. Three appendices are listed but not included.

The Health Hazard QA Guidelines for Assessing Army Systems (U.S. Army Health Hazard Assessment Office, 1989b, Appendix 1) is a cover memo for the HHA QA guidelines and gives a good overview of the HHA process. Although it does not provide specific procedures for the use of toxicity data in HHA, it provides better general guidance for the use of health hazard data (see section 4.d.3 of the document) than any other document under review.

In summary, the information submitted by AEHA did not specifically document a satisfactory QA process. While AEHA has many QA procedures in place, they deal more directly with specific techniques and procedures implemented after tests are selected and being conducted than with the choice of specific tests and test development. The QA responsibilities of the staff appear primarily to involve ascertaining that procedures are in place, are adequate for the task, and are followed. Peer review does not appear to be a part of the QA process. A periodic review by an outside group with QA experience may be beneficial. The development of a process for selecting appropriate toxicological tests will help to identify what kinds of data are needed when information is not provided by the selected tests.

Although AEHA priorities are established by its chain of command, review of procedures would help to establish consistency in the decision-making process as well as to enhance scientific credibility. Other organizations have adopted formal review procedures at various stages of the testing process, some of which might be applicable to AEHA.

In most of these organizations, peer review is provided by a group of independent scientists from government, academia, or industry. The peer review process often starts at the initial stages of designing the protocol and continues throughout the period of conducting the study, interpreting the results, and drafting the final report. The focus of such reviews is to assure that the protocol design is capable of addressing the purpose for which the material is being reviewed, that the conduct of the study is consistent with the protocol, and that the interpretation of the results is scientifically credible. In these organizations the staff responsible for the studies is available during the review to answer specific questions and to provide background information. In addition, the qualifications of staff scientists in some organizations are periodically reviewed to maintain a high degree of scientific credibility.

RECOMMENDATIONS FOR CATEGORY 1

The following recommendations were made by the subcommittee to enhance AEHA's decision-making process and scientific credibility:

(1) AEHA should develop a formal decision-making process for selecting specific toxicological tests to evaluate materials of interest.

(2) External, third-party audits of QA procedures should be initiated and repeated periodically.

SUBCOMMITTEE RESPONSE TO CATEGORY 3

The documents reviewed that are pertinent to this category included information on HHAs, HRAs, and MSRs. The HHA involves the identification, quantification, and assessment of toxicological hazards associated with new Army equipment. It was unclear from the documents reviewed whether a process is in place to review existing equipment. The HRA, while similar in content to the HHA from a toxicology perspective, addresses toxicological hazards associated with site-

specific, environmental restoration projects. From a practical standpoint, in many HHA and HRA projects, toxicological or exposure data are insufficient to support a complete assessment.

Primary responsibility for an HHA or HRA is assigned to a particular AEHA division on the basis of a request by the Office of the Surgeon General, depending on the major problems to be addressed. An HHA team is assembled to identify data gaps and to recommend means by which they can be filled. The Toxicology Division project officer participates in AEHA's HHA and HRA processes as a team member. Other team members may include physicians, audiologists, industrial hygienists, environmental engineers, and health physicists.

The review of MSRs proceeds differently. Rather than having an interdisciplinary team assume primary responsibility, the Toxicology Division staff assumes such responsibility.

Most of the documents covered in this section give broad guidelines and administrative details for conducting HHAs but do not provide specific procedures for the use of toxicity data. In its review, the subcommittee was less concerned with administrative procedures for HHAs but rather looked for information on how toxicology data were used in these assessments.

The Standard Operating Procedure for Toxicity Clearance (also covered in Category 1) addresses procedures and responsibilities, but does not give information about how decisions are made.

The Standardization Document Review (AEHA, 1987b, Appendix 1) gives a brief description of the Toxicology Division's role in the review process for documents that address military and federal specifications and standards. This description refers to a DOD directory that assigns broad areas of responsibility for such reviews but does not cite any standard operating procedures within the AEHA review process. This internal memorandum is not identified in terms of authority or distribution.

The HHA Program (U.S. Army, 1983, Appendix 1) gives broad guidelines for HHA, with specific areas of responsibility. It is difficult to follow, due to its use of numerous abbreviations and the style in which it is written. It appears that the quality of the HHA is highly dependent on professional expertise of the team assembled to accomplish a given assignment. The subcommittee was concerned that qualifications required for professional personnel were not clearly defined. Appendix D of the document gives risk assessment codes (RACs). It is important to note that the RACs are only as sound as the data used in developing the ratings.

The HHA Questionnaire (AEHA, Undated(d), Appendix 1) is a routine questionnaire to help with data collection.

The 1985 memorandum (AEHA, 1985, Appendix 1) provides an interpretation of the report on the HHA Program and outlines the policies, procedures, and responsibilities for the implementation of the HHA. The document describes how to accomplish the HHA logistically but does not describe conditions to be met in the process of developing it. Appendix B describes procedures for meetings of health hazard working groups, and Appendix C gives procedures for writing HHA reports. However, the actual quality of the HHA may be entirely dependent on the group of experts assembled to accomplish it, and there is no indication of consistency from one HHA to another.

The Appendix FF report on HHA projects (also covered in Cateory 1, Task 2) appears to be a guidance document from the directorate of industrial hygiene that addresses HHA reports. As in the 1985 AEHA memorandum and other documents provided by AEHA, it indicates that the project officer should ensure that "all potential health issues are addressed." However, none of the documents provides any indication of which health hazards are considered and how decisions are made about which ones are relevant in a given situation.

The report "Candidate Safe Smoke Formulations" (AEHA, 1989d, Appendix 1) is an HHA report. It appears to have been prepared by the AEHA Toxicology Division. A guidance document for development of this type of report does not appear to exist. No assessment or comparison is made of the toxicity of the original material with the toxicity of those chemicals under consideration as substitutes.

The memoranda on disposal instructions (AEHA, 1989e,f, Appendix 1) are a completed request for toxicity data and response from the Toxicology Division to dispose of materials appropriately. Input from the Toxicology Division did not require a significant effort. It is likely that this type of request is made to them on a regular basis. The request was vague but asked for instructions for the disposal of carcinogenic, mutagenic, or cytotoxic substances. The Toxicology Division provided only the classification from the International Agency for Research on Cancer for the carcinogenic risk of the compounds listed.

Other reports listed in Appendix 1 were provided as examples of reviews of MSRs conducted by AEHA's Toxicology Division (AEHA, 1981, 1989g-j, Undated(e); U.S. Army Troop Support Command, 1989a,b; U.S. Army Natick Research Development and Engineering Center, 1989). Although the documents provided detail on specifications and physical parameters for water jugs and women's pants, they

did not appear to address potential hazards from chemical components or to conduct risk assessments. The first four items listed in this paragraph, for example, identify plastic components of the jugs but do not mention the possibility of plasticizer migration into the drinking water. Likewise, the remaining items identify dyes for pants components but do not discuss their toxicity or potential for migration. In both cases, defining the toxicity and addressing the migration of the chemical components are necessary to evaluate the risk and place it in perspective. In general, a systematic process for review of these types of requests does not appear to exist within AEHA's Toxicology Division, nor is there an obvious system to audit the quality of the reviews made by the Toxicology Division.

There are several methods for identifying the potential hazard of chemical materials. This is usually accomplished by a review of the available and pertinent epidemiological and toxicological literature and subsequent toxicity testing and other testing conducted as necessary. Such studies may address absorption, metabolism, and pharmacokinetics. While hazard assessment is often conducted internally by personnel within AEHA, it is useful to have an external peer review of the internal interpretations to confirm that the conclusions are supportable.

Risk assessment is a complex process. It is not the purpose of this document to detail the risk assessment process. Some of the published guidelines on the subject are listed in Appendix 2. Using the National Research Council paradigm (NRC, 1983), it becomes clear that risk characterization is dependent upon hazard assessment. In general simplistic terms, hazard refers to the inherent toxicity of a given chemical material, while risk combines this information with data on dose-response, exposure, or the potential for exposure to estimate the probability of an adverse outcome. For example, a chemical can be extremely hazardous, but if there is no potential for exposure, it does not present a risk.

Risk assessment is usually conducted best with consideration of the "total weight of the evidence." In many cases, decisions must be made with limited data. This factor pertains especially to human exposure information. Therefore, assumptions must be made often when data are not available. These assumptions lead to considerable uncertainty in the decisions and indicate the need for thorough documentation and independent peer review.

Risk assessments are of limited value unless they are effectively communicated to interested parties. When presenting risk assessments,

it is important to focus the information on the audience. By knowing the audience, one can do a better job of relating the findings in a format that will be of most use to it. In many cases, the audience (e.g., risk managers) may not be trained in the health sciences, and risk assessments must be communicated in nontechnical or lay terms. Sensitivity to this need helps to preclude miscommunication and, in turn, misuse. In this regard, a resource of particular value is *Improving Risk Communication* (NRC, 1989).

RECOMMENDATIONS FOR CATEGORY 3

The following recommendations were made by the subcommittee to enhance AEHA's process on HHAs:

(1) The subcommittee recommends that AEHA establish procedures for determining the areas of expertise required on the HHA teams and selecting individuals who are qualified to accomplish the task. This recommendation is made to ensure uniformity and high quality of HHAs.

(2) Procedures should be established to determine the types of toxicity to be evaluated in HHAs (e.g., acute, subchronic, chronic, carcinogenicity, mutagenicity, reproductive and developmental toxicity, neurotoxicity, and immunotoxicity) and the toxicity data required in each area. The procedures for using such data in the HHA need to be specified.

(3) Some form of independent review of procedures should be established to enhance the scientific credibility of AEHA toxicology evaluations. The subcommittee realizes that Army requirements may limit the use of such an open process, but it also believes that an independent review of testing requirements is possible and highly desirable.

4 *Establishment of Peer Review Procedures*

The subcommittee recommends the establishment of a peer review panel for the Toxicology Division's activities. In addition, the subcommittee recommends that a science advisory board for AEHA be established to assist the agency in carrying out its mission and in the continuum defined in Chapter 2.

In view of the fact that the Toxicology Division staff cannot include experts on all aspects of toxicology, the subcommittee recommends that staff members be strongly encouraged to call on consultants.

The peer review panel should be composed of specialists in various areas of toxicology. Specialists in appropriate areas should be called on an ad hoc basis to review and recommend specific study protocols. They are then called upon periodically to review the progress of the study and finally to review the results and report. Every study should have at least two peer reviewers. They should be recruited outside of the organization and be free from conflict of interest. Peer review reports should be submitted in writing and the responsible project officers should respond in writing.

The science advisory board should consist of scientists of stature from academia, industry, and government in those fields related to the science and technology of environmental health and toxicology. The board would have to be chartered in accordance with appropriate federal procedures. It will be the function of the board periodically to review the program(s) of the AEHA to assure that programs are appropriate to the charge of the agency. The science advisory board would give broadbased advice on matters such as the organization, technological approaches, and future planning to assure that the program keeps abreast of the advancing field of toxicology. In addition, it would oversee the peer review process, review and oversee the QA program for AEHA and its Toxicology Division, review AEHA programs to assure the highest scientific competence, evaluate priority setting procedures, review the publication process, and recommend

program improvements. The comments and advice of the Science Advisory Board should be submitted as written reports.

The subcommittee believes that the establishment and use of advisory groups and ready access to consultants would strengthen the agency's ability to perform its mission to the Army and would lend credence to its conclusions and recommendations.

Charters for science advisory boards for the National Center for Toxicological Research, the National Toxicology Program, and the Environmental Protection Agency are examples of how other government agencies establish and use science advisory boards.

RECOMMENDATIONS

The subcommittee recommends that AEHA establish two groups of outside advisors: a peer review panel for the Toxicology Division and a science advisory board for AEHA. Both groups would provide expertise and perspective on the scientific, technical, and service aspects of the agency's toxicology program. Areas of expertise that should be represented in groups of outside advisors include toxicology, occupational and environmental medicine, industrial hygiene, ergonomics, epidemiology, biostatistics, health physics, and environmental sciences.

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Appendix 1

DOCUMENTS PROVIDED BY AEHA AND REVIEWED BY THE SUBCOMMITTEE ON THE AEHA TOXICOLOGY PROGRAM

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AEHA (U.S. Army Environmental Hygiene Agency). 1989j. Internal Memorandum. Subject: Proposed Military Specification MIL-S-43526D, Slacks, Utility, Womens, Wool, Field, Project Number 8410-0697.

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Appendix 2

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